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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/225,718	01/06/1999	DOUGLAS A. TRECO	07236/013004	1979

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EXAMINER	
KETTER, JAMES S	

ART UNIT	PAPER NUMBER
1636	28

DATE MAILED: 02/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

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Commissioner of Patents and Trademarks

--See attached--

Office Action Summary	Application No.	Applicant(s)	
	09/225,718	TRECO ET AL.	
	Examiner	Art Unit	
	James S. Ketter	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-168* is/are pending in the application.

4a) Of the above claim(s) *66-113* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *114-168* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

Claims 66-113 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 15.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 114-168 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record set forth in Papers Nos. 16 and 20, mailed 29 January 2001 and 10 October 2001, respectively.

At pages 2 and 3 of the remarks filed 15 November 2002, Applicants argue that they believe that the use of the term "gene therapy' in reference to the claimed invention is problematic, alleging that it leads to overgeneralization. Applicants then argue that their position that the cited references are not relevant has been ignored or addressed without rigorous reasoning, and that the "successes" in the cited references have been ignored. Further along, Applicants argue that they "have supplied highly relevant evidence that the claimed methods would work", but that "the Examiner appears to believe that it is less persuasive than his own evidence that gene therapy in general has problems. First, it is maintained that the use of the term "gene therapy" is appropriate, as the claimed methods fit into what is widely known in the art as "ex vivo gene therapy". It is highly appropriate to view in and ex vivo gene therapy

together for purposes of determining the extent of enablement of the disclosure, where both types of therapy would logically encounter the same problems, in view of empirical findings known in the art. In other words, if the art has continually struggled with the problem of persistence of expression of recombinant cells after implantation into the patient, and references describing this general problem do not except ex vivo therapies, then it is entirely appropriate to apply such references to claims of the breadth of the instant claims. Where a reference notes an instance of successful, persistent expression of a therapeutic gene in a model system, or even in a patient, it must be taken as significant when the author of such a reference still reaches the conclusion that successful practice of gene therapy is hampered by lack of predictable, persistent expression of the inserted gene. These points as found in the cited references already have been made of record. Second, the evidence cited by Applicants, to try to demonstrate that persistent expression was enabled, represents 8 experiments or sources: 1) the implantation of transformed rabbit fibroblasts expressing hGH into nude mice (Example 9 of the '840 application); 2) phase I trials of transformed dermal fibroblasts taken from 6 patients and reimplanted after transformation, to express factor VIII (Roth et al., of record); 3) the reference in Anderson et al. to the presence of transformed circulating cells which had been implanted 7 years prior (although no showing of expression from the recombinant constructs in said cells was given); 4) claims issued in US Patent 5,968,502; 5) Page 1641 of Ferber, wherein Kay's experiment is discussed; 6) Miyoshi et al., cited in Mountain (of record); and 7) Nishi et al., cited in Mountain (of record). Each has been addressed on the record. It is maintained that these examples, even taken collectively, are insufficient to demonstrate enablement of the instant claims as of their effective filing date, as follows:

4) At pages 4-6 of the remarks filed 15 November 2002, Applicants argue that Claim 1 of US Patent 5,968,502, which is relatd to the instant application, encompasses the instant claims, and therefore the instant claims should be found to be enabled. However, patented Claim 1 is much more broadly drawn, in that there is no limitation to therapeutic proteins. For reasons of record in the present rejection, and as elaborated below, therapeutic expression of a protein from a recombinant construct in a cell implanted in a subject is a much higher technical hurdle to overcome than mere expression at whatever level, for whatever duration. Since it is well-established law that an Applicant need not exemplify each and every embodiment encompassed within a claim, it is apparent that a more narrowly drawn claim, even though encompassed by the enabled broad claim, might cover only subject matter for which a sufficiently enabling disclosure was not present. Since each case is examined upon its own merits, the finding of enablement for the broader patented claim does not require a finding of enablement for the narrower instant claims.

1) At pages 8 and 9 of the remarks filed 15 November 2002, Applicants argue that there was no evidence provided that animal models are not well-accepted as models for human gene therapy methods, saying that the Examiner had merely stated opinion. However, Orkin et al. (of record) was cited in support. In response to this, Applicants argue, at page 9, that Orkin et al. is irrelevant, as it is drawn to in vivo gene therapy. It is pointed out here that this represents a blanket dismissal of evidence, based solely on the argument that Orkin et al. is not as close to the claimed invention as some of the examples cited by Applicants. However, this is unpersuasive. Orkin et al. discusses both in and ex vivo methods, and teaches that animal models are of limited value in testing gene therapy methods. Applicants have not refuted this view in the art, but

merely argued that Orkin et al. is not applicable. Whatever the distance may be between Orkin et al. and the claimed invention, both fall within the art of gene therapy, and thus Orkin et al. must be considered in the balance as a general reference. Applicants have not provided a teaching of the general and unqualified acceptance of animal models in gene therapy, but have relied on specific examples of success. These examples, discussed of record and further below, are not commensurate in scope with the claimed invention, while Orkin et al. at least comments generally and with respect to both in and ex vivo methods. Going back to page 8 of the response, it is noted that Applicants argue that the immune-incompetent status of nude mice does not reduce their value as a model system. However, in the passage form '840 cited at page 8 of the response, it is clear that the immune-incompetence of these cells permits the long-term survival of the cells in vivo. As such, the system is not a representative one of the normal immune-competent patient, as the factor of immune response id removed as a variable. While it is understood that the reasons for using such cells were based upon the solution of an experimental design problem, it stands that the immune-incompetence of nude mice represents a variable not present in (most) clinical situations.

At page 10, Applicants argue that only viral vectors and other methods outside the claims were referred to with respect to the statement that not all expression in ex vivo methods is transient. Applicants extend this, arguing that transient expression may be useful, and arguing that the Examiner did not respond to this point. However, if transience were not the issue, then no response would have been needed. To the extent that transient expression is the issue, the references of record have already been shown to teach that lack of persistent expression has been a barrier in gene therapy generally. Furthermore, it must be noted that if some transient systems

would be usable for gene therapy methods, particularly the present invention involving ex vivo methods, it is not clear which methods would result in transient expression and which would result in persistent expression. It is apparent that it is to this point of unpredictability that the prior art references refer in teaching that a lack of persistent expression is a technical problem yet to be solved in order to generally practice gene therapy.

2) From the paragraph bridging pages 10 and 11, it would appear that Applicants did not correctly understand the point about trail-and-error experimentation leading to the Roth et al. experimental protocol. The point was that the protocol used in Roth et al. would not have been present as such in the instant specification. To have gone from the specification as filed to the details of the protocol used by Roth et al., one of skill would have required either teachings from the instant specification, teachings from the prior art, or a combination of the two, to avoid the need for empirical experimentation. However, at the time of filing of the present invention, it is not apparent that such teachings were present in the art, and it is not clear where they might have been found in the specification. As such, empirical experimentation would have been required to develop the protocol of Roth et al., and in the absence of guidelines or teachings of a specific nature, such experimentation would have been trial-and-error.

At the first full paragraph of page 11, Applicants argue that Roth et al. is more than merely one experiment. However, it represents a disclosure that is not commensurate in scope with the claimed invention. Applicants then state "it stands in stark contrast to the complete lack of any studies of comparable relevance to support the Examiner's position." However, Applicants must realize that they ask for a type of evidence that presumably could not exist—an explicit teaching that the methods claimed by the present Applicants cannot be practiced.

Applicants' invention is presumed to be novel and unobvious over the art. Who but Applicants would have conducted such a trial, and were it conducted, why would it have been published? Instead, the instant rejection is based upon more general teachings in the art that illustrate the state of the art, unpredictability of the art, the lack of success, i.e., guidelines and examples to be followed, and so forth. Were the standard for showing a lack of enabling disclosure to be the citation of a reference showing a direct refutation of the practicability of claimed invention, then 35 USC § 112, first paragraph with respect to enablement, would be without purpose.

5) At page 11, second full paragraph, Applicants argue that Ferber et al. was referring only to in vivo gene therapy methods, e.g., as performed by Kay. However, it is not clear how this is apparent from the context—rather, it is noted that the comment is made after a description of, and thus in view of Applicants' own work. Thus, it would not seem that Ferber viewed the persistence of expression problem as generally solved. Furthermore, he teaches that lack of persistence has been in part due to the lack of integration of the vector into the genome—clearly, he recognized that other factors must be considered.

At the paragraph bridging pages 11 and 12, Applicants argue that table 4 of Mountain does not comment upon ex vivo methods. Applicants argue that the integration methods are not associated with short duration of expression. However, at pages 123 and 124, mountain discusses the three types of non-viral gene therapy. In discussion of each, ex vivo methods are mentioned, making it clear that the short duration of expression problem cited is and was applicable to methods akin to Applicants' invention. As such, the content of Table 4 is clarified. Furthermore, at page 125, right-hand column, first through third full paragraphs, Mountain makes clear that persistence of expression is poor even for integrating vectors.

6) With respect to Miyoshi et al., the long duration of expression seen in Miyoshi et al. was, again, in immune-compromised mice, was based on a viral vector system, and involved human cells implanted in said mice, which is unlike a clinical gene therapy method. Furthermore, Miyoshi et al. is a post-filing date reference that represents a single experiment not commensurate in scope with the claimed invention.

7) With respect to Nishi et al., there seems to be little or no data to determine the success of the disclosed experiments. Furthermore, the vector appears to be based on a replicon (EBV) and thus does not at all address the question of persistence of expression of an integrated gene, let alone a non-viral one.

3) Applicants call for a clarification of the applicability of Anderson (of record), at page 12, second full paragraph. At page 25, right-hand column, it is taught that retroviral vectors are primarily used in ex vivo protocols. Then, at page 26, right-hand column, first and second full paragraphs, it is taught that long-term gene expression is problematic in gene therapy methods (first full paragraph) and that deactivation of the genes or death of the cells usually occurs (second full paragraph.) The second full paragraph also discusses retroviral vectors, linking these discussions. Since retroviral vectors are nearly always used in ex vivo protocols, the logic follows that ex vivo gene therapy protocols suffer from a lack of persistent expression.

At the paragraph bridging pages 12 and 13, Applicants point to the comment in Anderson with respect to the ADA cases. However, a careful reading of Anderson shows that ADA was still being administered, and that the persistence of the cells carrying the construct was established, but no implication or teaching is present indicating that the health of the subjects

was due to any level of expression of ADA (which does not appear to have been measured); hence Anderson's statement that no definitive conclusions can be drawn.

At the full paragraph at page 13, Applicants appear to ask for examples of conditions that could not be treated without long-term, predictable expression of the gene in question. However, it is clear from the discussion of the art in the two previous Office Actions and in the Advisory Action, as well as the present Office Action, that the art has recognized that the gene therapy art as of the time of filing, and even at the time of the cited references, was not developed to the level where any disease state could be treated effectively, primarily due to the unpredictability and lack of persistence of expression of the gene in question. Thus, it follows that known disease states were generally not amenable to treatment as of the filing date of the invention, as it has not been persuasively argued that the claimed invention would not have suffered the same problems. If, by asking for examples of conditions for which practice of the claimed invention would not be enabled, Applicants are asking that, in effect, a scope of enablement type rejection be made, in response it is maintained that the present rejection is proper, and that no embodiment of the instant claims is enabled. Applicants then "question the Examiner's expertise in judging the usefulness of therapies of varying durations." While it is not clear exactly what Applicants are questioning, it is taken that they disagree with the position that lack of persistent expression is and was a known barrier in the art to useful gene therapy methods. This point has been addressed on the record and above. Applicants then ask why repeated treatments with transformed cells would not be enabled. However, it is noted that this remedy does not seem to have been accepted by the art, in view of its absence from the cited references. Furthermore, it is not apparent that the instant specification teaches such an adaptation. And, again, as set forth

above, if some transient systems would be usable for gene therapy methods, particularly the present invention involving ex vivo methods, it is not clear which methods would result in transient expression and which would result in persistent expression. It is apparent that it is to this point of unpredictability that the prior art references refer in teaching that a lack of persistent expression is a technical problem yet to be solved in order to generally practice gene therapy. It is believed that this addresses Applicants' arguments in the paragraph bridging pages 13 and 14, as well. Furthermore, it is believed that each of Applicants' points of argument summarized at page 14 has been addressed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to the directly to the Examiner by facsimile transmission at (703) 746-5155. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993)(see 37 CFR ' 1.6(d)). To send the facsimile to the Art Unit instead, the Art Unit 1636 Fax number is (703) 305-7939. NOTE: If Applicant does submit a paper by fax to this number, the Examiner must be notified promptly, to ensure matching of the faxed paper to the application file, and the original signed copy should be retained by Applicant or Applicant's representative. (703) 308-4242 or (703) 305-3014 may be used without notification of the Examiner, with such faxed papers being handled in the manner of mailed responses. Applicant is encouraged to use the latter two fax numbers unless immediate action by the Examiner is required, e.g., during discussions of claim language for allowable subject matter. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the Examiner with respect to the examination on the merits should be directed to James Ketter whose telephone number is (703) 308-1169. The Examiner normally can be reached on M-F (9:00-6:30), with alternate Fridays off.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Remy Yucel, can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Jsk
February 20, 2003

JAMES KETTER
PRIMARY EXAMINER